Mission Possible: How FDA Can Move at the Speed of Science

Report of the Science Looking Forward Subcommittee

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FDA Mission Statement

FDA is responsible for protecting the public health by assuring the safety, efficacy and security of human and veterinary drugs, biological products, medical devices, our nation's food supply, cosmetics, and products that emit radiation.

FDA is also responsible for advancing the public health by helping to speed innovations that make medicines more effective, safer, and more affordable and by helping the public get the accurate, science-based information they need to use medicines and foods to maintain and improve their health. FDA also has responsibility for regulating the manufacturing, marketing and distribution of tobacco products to protect the public health and to reduce tobacco use by minors.

Finally, FDA plays a significant role in the Nation's counterterrorism capability. FDA fulfills this responsibility by ensuring the security of the food supply and by fostering development of medical products to respond to deliberate and naturally emerging public health threats.

Members of the Science Looking Forward Subcommittee

Margaret Anderson, MS
Executive Director,
FasterCures

Gail H. Cassell, PhD
Senior Lecturer, Dept. of Global Health and Social Medicine, Harvard University
Senior Scientist, Division of Global Health Equity,
Brigham and Women's Hospital

Maria C. Freire, PhD
President and Executive Director,
Foundation for the NIH

Lynn R. Goldman, MD, MPH
Dean and Professor of Environmental & Occupational Health,
School of Public Health and Health Services,
The George Washington University

Peter K. Honig, MD, MPH
Senior Vice President and Head of Worldwide Safety and Regulatory,
Pfizer, Inc.

Frederick Kushner, MD
Medical Director,
Heart Clinic of Louisiana
Clinical Professor of Medicine,
Tulane Medical School

Mark R. McLellan, PhD
Vice President for Research and Dean of the School of Graduate Studies,
Utah State University

Barbara J. McNeil, MD, PhD
Ridley Watts Professor and Head,
Department of Health Care Policy,
Harvard Medical School

Martin A. Philbert, PhD *(Chair)*
Dean and Professor of Toxicology,
School of Public Health,
University of Michigan

Bruce M. Psaty, MD, PhD, MPH
Professor of Medicine and Epidemiology,
Co-director, Cardiovascular Health Research Unit,
University of Washington

Alan J. Russell, PhD
Highmark Distinguished Career Professor,
Carnegie Mellon University

Ellen Sigal, PhD
Chairperson,
Friends of Cancer Research

Executive Summary

Introduction

In 2013, the Commissioner of Food and Drugs charged the Food and Drug Administration's (FDA's) Science Board, an advisory committee of national experts across various scientific disciplines, to make recommendations on areas deemed critical to the Agency's ability to carry out its scientific mission:

1. How FDA can meet emerging and future trends in science and technology
2. How FDA can better use collaborations to advance its mission and
3. How FDA can support a culture of scientific excellence and creativity.

The Science Looking Forward Subcommittee was created to evaluate these three principal areas. The Subcommittee was also asked to assess progress since the Science Board's 2007 *FDA Science and Mission at Risk* report (*"Mission at Risk"*), which made recommendations to address serious impediments at that time. Some of the most significant conclusions from the 2007 report were:

- FDA could not fulfill its mission, due to a weak scientific base and inadequate scientific workforce
- A disparity between FDA's responsibilities and resources seriously threatened the Agency's ability to perform its mission
- FDA did not have the capacity to ensure the safety of the nation's food supply and
- FDA's ability to ensure the rapid entry onto the market of life-saving new medical therapies – especially those resulting from new and emerging technologies – was highly doubtful.

The 2007 report and its conclusions were broadly considered at the time by the scientific and medical communities to be an important assessment of FDA's capabilities and a valuable roadmap for FDA-wide improvements – and were also well received by Congress and the public at large.

Progress Since 2007

The responsiveness of FDA to the *Mission at Risk* report and those responsible for overseeing its work has been extensive, transformative, and laudable. Many substantive changes have been made in FDA's organization, authorities, and programs that significantly address issues identified in 2007. Some of the most notable are:

- Creation of the Office of the Chief Scientist with the remit to ensure better coordination and promotion of FDA's science, which, in turn, includes new offices focused on the support of regulatory science, health informatics, the professional development of

Agency scientists, scientific integrity, minority health, and a group devoted specifically to countermeasures for acts of terrorism and emerging threats.

- New statutory authority from Congress that not only improves FDA's ability to tackle public health problems but also increases Agency responsibilities – including the authority to regulate cigarettes and other tobacco products; a new food safety system that moves FDA from an antiquated system of food safety protection to a new, science-based approach that relies on preventive controls in food production; new authorities to expedite the review of generic drugs and to better protect the public from imported drugs; a new regulatory paradigm for drugs manufactured ("compounded") by pharmacies; and new regulatory strategies for the market entry of "biosimilar" drugs. Additionally, FDA established offices in foreign countries, including in China and India, to strengthen oversight of the supply chain and imported products.
- Initiatives across FDA programs to deal with important new and emerging technologies, such as (but not limited to) stem cells, 3-D printing, predictive toxicology, genome sequencing and computer simulation.
- A Precision Medicine Initiative, in coordination with the National Institutes of Health (NIH), that promises to revolutionize medicine by developing new therapies based on the genetic makeup of patients or their diseases.
- Advances in regulatory science that promote the lifecycle approach to regulation for both approvals and the postmarket evaluation of the benefit-risk profile of drugs, devices, and biologics during their entire time on the market.
- Increased focus on active postmarket surveillance, primarily in the form of the new Sentinel active surveillance system, which will draw on existing health care data (such as reimbursement claims) to continuously monitor the safety of medical products.
- Increased funding, from both appropriations by Congress and appropriate user fees paid by industry activities, which has enabled FDA to increase its capabilities in several areas (although significant deficits remain in others); and funding for FDA to substantially meet an almost half-century-long goal of establishing a centralized campus with state-of-the art laboratories.
- Intra-Agency initiatives and extramural programs and partnerships that enabled FDA to meet the eight scientific priorities identified in the Agency's Strategic Plan for Advancing Regulatory Science[1] in 2011 (and a ninth priority area, Strengthening the Global Product Safety Net[2], added in 2013).[3]

[1] Available at: http://www.fda.gov/ScienceResearch/SpecialTopics/RegulatoryScience/ucm267719.htm. Accessed on Sept. 9, 2015

[2] Available at: http://www.fda.gov/scienceresearch/specialtopics/regulatoryscience/ucm452830.htm, Accessed on Sept. 9, 2015

[3] These programs and collaborations are enabled by novel vehicles such as the Centers of Excellence in Regulatory Science (CERSIs) and the Broad Agency Announcement (BAA), established by FDA in 2011 and 2012, respectively, through well-established mechanisms such as grants, contracts and Cooperative Research and Development Agreements (CRADAs) and by the formation of unique public-private partnerships and consortia like the Medical Device Innovation Consortium (MDIC).

Looking Forward

While the improvements in FDA's capabilities since 2007 are substantial, the Subcommittee has identified a range of concerns that are new or have not been adequately addressed since the release of the *Mission at Risk* report. They are summarized below.

Medical Product Innovation

The Subcommittee notes that improvements in the review of new medical products have been steady and impressive. Indeed, FDA reports that over the past two decades, the time required for FDA review of new drugs has decreased from years to months and that the Agency has become the acknowledged leader among the world's regulatory agencies in both the number of new drugs approved each year and in the timeliness of review.[4]

Similar improvements in streamlining review processes are underway for medical devices. The result has been expedited access to patients for life-saving new therapies and an innovative, highly competitive biomedical industry in the United States.

However, the Subcommittee recognizes that patients and industry alike are concerned about FDA's ability to support biomedical innovation. Thus, the Subcommittee identified a number of areas in which FDA can and should be better prepared to stimulate biomedical innovation, including:

- Facilitating the qualification of biomarkers, including surrogate endpoints, for evaluation of new therapies and providing guidance on how new biomarkers can be qualified as surrogate endpoints
- Increasing the efficiency and lowering the cost of clinical trials by facilitating the development and encouraging the use of clinical trial networks and master protocols
- Expanding ongoing access to external experts in emerging technologies to help accelerate approvals
- Using new data-mining and analytical tools to evaluate the efficacy and safety of new medical products, including full deployment of FDA's Sentinel Initiative and its expansion to medical devices

Food Safety and Applied Nutrition

Enactment by Congress of the Food Safety Modernization Act was the most significant advance in food protection since the passage of the original Food, Drug and Cosmetic Act in 1938. To successfully protect the food supply by implementing the new law, FDA must re-train its inspectors in the latest scientific methods, help states adopt similar science-based inspection protocols, recruit more experts in food science, and require, for the first time, that foreign producers of food destined for the United States meet the same safety criteria as domestic

[4] Targeted Drug Development: Why Are Many Diseases Lagging Behind? Available at: http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Reports/UCM454996.pdf. Accessed on Sept. 14, 2015[5] CBO estimate of costs of S.510, August 12, 2010.

producers. The Congressional Budget Office has estimated that FDA will need almost $600 million in additional funding to accomplish this daunting task,[5] but Congress thus far has provided only a fraction of the needed resources.

In the nutrition area, about 400,000 deaths in the United States each year are attributed to poor diet and inactivity.[6] The Subcommittee believes that FDA is positioned to improve the health of the public by helping to address these chronic diet-related problems through FDA's nutrition authorities.

Chemical contaminants in food is of increasing public concern, caused in part by increasing consumer exposure to various food components, such as food additives, pesticides, and heavy metals; the safety of cosmetics ingredients also is a growing concern. The Subcommittee is concerned about the weaknesses in FDA's food program and recommends that FDA undertake a series of actions:

- Conduct targeted regulatory science research to develop hazard mitigation strategies or preventive controls
- Expand FDA's under-resourced nutrition initiatives to empower the consumer to make the best nutritional choices
- Incorporate the latest behavioral science into FDA's food program, so that it can adopt the latest scientific procedures for understanding how to help consumers improve their diets and thus reduce the toll of chronic, diet-related disease
- Enhance initiatives to improve monitoring exposure to food components and contaminants, including tracking exposures over time, screening methods for the detection of chemical and microbiological contaminants in food and animal feed, and integrating and applying modern toxicology to predict risk from such contaminants.

Product Manufacturing and Quality

The Subcommittee notes with concern that medical product and food manufacturing quality control procedures have not kept pace with the advances being made in research and product development, and that more research is needed in such areas as product design, manufacture, and quality assurance. Examples of improvements that should be made include:

- Expand use of the latest DNA technology to characterize medical products, including vaccines, and to ensure their purity and safety
- Expand use of the latest DNA technology to identify the source of foodborne disease outbreaks

[5] CBO estimate of costs of S.510, August 12, 2010.
[6] Mokdad AH, Remington PL. Measuring health behaviors in populations. Prev Chronic Dis 2010; 7(4):A75. Available at: http://www.cdc.gov/pcd/issues/2010/jul/10_0010.htm. Accessed Sept. 9, 2015.

- Expand use of appropriate analytic methods for assessing purity of products made using nanotechnology
- Equip field staff with novel technologies for laboratory and field analytical procedures to evaluate high-risk medical devices

Modernizing Toxicology

Across most of FDA's programs, toxicology is critical to the Agency's ability to predict product safety or assess the significance of chemicals used in foods, pharmaceuticals, vaccines, and other FDA-regulated products. Much of FDA's toxicology effort today is derived from decades-old principles and approaches. FDA has taken significant steps toward modernizing its toxicology programs, but the Subcommittee concludes that much work remains to be done and FDA should adopt the latest technologies to identify and qualify biomarkers of toxicity, including:

- Induced pluripotent stem cells to produce cell types for evaluation of toxicity
- Bioimaging coupled with cognitive and functional testing to help determine neurotoxicity
- Mathematical modeling of cells and physiological systems
- Improved methods of *in silico* modeling to identify patient-specific susceptibilities to individual drugs
- Organ-on-a-chip technology to study toxicities, such as drug-induced pancreatitis

Extramural Programs and Collaborations

To be maximally effective, a science-based agency such as FDA must be able to use the scientific expertise and advice of the broader scientific community by leveraging the human, financial, and scientific resources of industry, academia, the health care system, and other government agencies.

FDA has successfully used collaborations with these communities in a host of ways in the past, and the report details several of those successes (e.g., the Medical Device Innovation Consortium, a public-private partnership that has supported innovation in new medical devices while demonstrating ways of lowering the costs of device development).

Nevertheless, the Subcommittee concluded that much more can and should be done to develop extramural programs and external collaborations. In particular, the Reagan-Udall Foundation, which was created by Congress in response to the 2007 *Mission at Risk* report, can be a focal point for FDA in establishing and nurturing such collaborations. Thus, the Subcommittee has proposed recommendations to help FDA further this effort, which the Subcommittee believes must be an Agency imperative, including:

- Taking a more assertive posture in identifying and designing new partnerships, especially by bringing into play research universities and research-supporting foundations, and using the Reagan-Udall Foundation as a catalyst for those new initiatives
- Establishing a "portfolio" approach to extramural collaborative alliances, setting priorities, and matching specific collaborations to Agency objectives and scientific needs
- Identifying structural hurdles to more effective collaborations, including legal, policy, or conflict-of-interest; and developing plans to seek statutory or policy change to overcome those hurdles
- Ascertaining the level of increased funding needed to effectively increase collaborations, and making enhanced funding a priority

Recruiting a 21st-Century Scientific Workforce

A major concern articulated in the 2007 *Mission at Risk* report focused on FDA's ability to recruit and retain outstanding scientists. FDA has clearly improved its efforts in this regard. Yet, while continuing scientific and professional training programs, for example, have been implemented, barriers to adequate training remain, as do those for recruitment and retention.

Restrictions on pay have reduced the applicant pool for important FDA positions, and an archaic and ponderous Human Resources (HR) system has further impeded FDA's ability to recruit outstanding talent. Therefore, the Subcommittee urges FDA to take steps to improve recruitment and retention, including:

- Seek "Direct Hire Authority" for scientific staff for a period of no less than five years, so that FDA can fill current vacancies more rapidly without having to fulfill the cumbersome and time-consuming procedures required by current civil service hiring authorities
- Seek authority to offer special pay levels, up to that of the President, to outstanding and senior scientists whom the Agency cannot now recruit due to restrictions on Federal pay
- Expand the use of existing special pay authorities, such as Title 38 and Title 42
- Implement expanded retention pay for hard-to-recruit specialists, such as specialty physicians, biomedical engineers, biostatisticians, and toxicologists
- Investigate and implement mechanisms that enable increased pay, bonuses and/or awards for outstanding scientists already employed at FDA
- Ensure that FDA scientists are given the training and continuing education opportunities to keep up with the state of the art in their disciplines, including a relaxation of the rules limiting attendance at scientific conferences that will enable them to do so

Resources to Match Responsibilities

The Subcommittee is gratified that the Administration and Congressional responses to the *Mission at Risk* report were in apparent agreement with its conclusions about FDA resources and that new resources were subsequently provided from both appropriations and user fees for medical product reviews. Indeed, shortly after the report's issuance, the Administration proposed – and Congress acceded to – a multi-million dollar special appropriation that restored budget cuts from earlier years.

Moreover, additional user fees for drug, biologic and medical device reviews were approved by Congress, as well as new user fees for the regulation of tobacco, to oversee a biosimilars review program, for the review of generic drugs, and for increased oversight of imported drugs. However, several resource deficits exist that the Subcommittee believes threaten FDA's ability to advance in the future:

1. Congress is considering legislation – known as *21st Century Cures* – that will impose significant new demands upon FDA in its regulation of drug, biologic, and medical device products. The Congressional Budget Office has estimated that the House of Representatives' version of this legislation will impose costs in the neighborhood of $1 billion on FDA over the first five years after enactment.[7] Although the House bill has a provision for partial funding of those costs, even that partial funding is uncertain. Therefore, the Subcommittee expresses its strong opinion that an unfunded mandate of that magnitude could set back the progress of medical product development by forcing FDA to divert its scientific staff away from its currently successful review programs, thus harming patients and the progress of biomedical innovation.
2. As noted earlier, the enactment of the Food Safety Modernization Act creates a new, science-based system of foodborne disease prevention that is expected to save the United States economy tens of billions of dollars a year.[8] The President has proposed additional resources, including an increase of about $110 million of new budget authority in his FY 2016 budget request, and the Subcommittee would like to join with the food industry and consumer groups who strongly support those additional resources.
3. The efforts to leverage external collaborations and to recruit outstanding scientific staff will require new resources.
4. Additionally, the Subcommittee recommends that FDA request new funding in three important areas to: 1) provide the necessary resources in the Office of the Chief Scientist to coordinate the allocation of core scientific capabilities, 2) modernize toxicology and bioinformatics, and 3) conduct studies of generic drugs to answer major drug safety questions.

[7] CBO report on cost estimate of H.R. 6, June 23, 2015
[8] Journal of Food Protection, January 2012, pp. 123-131

Conclusion

The Subcommittee is pleased to note that FDA has made significant strides in strengthening its scientific capabilities in response to the 2007 *Mission at Risk* report. Its drug review program is a global leader in both speed and quality of review, the focus on improving its science infrastructure is to be applauded, and the new food safety legislation promises to bring a new scientific focus on food protection that will greatly reduce foodborne illness.

Nevertheless, medical and technological advances continue to occur at a steady and relentless pace, and FDA must stay abreast if it is to remain the preeminent public health agency that the public expects. To do that, the Subcommittee urges FDA leadership to embrace the findings and recommendations embodied in this report, which are targeted not on changing the organization but on strengthening it for the challenges ahead.

Background

Despite its relatively small size, the Food and Drug Administration (FDA) continues to have disproportionately large responsibilities for and impacts on the health and well-being of the American public. Its scientific research and regulatory actions touch the lives of every American many times each day, ensuring that the food we eat is safe, that medical and veterinary products are safe and effective, and that product innovations are speedily advanced.

Products regulated by FDA constitute a large portion of the U.S. economy – estimated at 20 cents of every dollar spent by American consumers.[9] And even though FDA is responsible for regulating a vast list of products and implementing policies, few appreciate that Congress regularly adds new regulatory responsibilities, often without concomitant resources to meet the new demands on the Agency.

As a science-based regulatory agency, FDA must rely on its scientific credibility which, in turn, depends on its staff's capabilities. Importantly, scientific advancement at FDA offers opportunities to save lives and positively affect our economy.

However, the complexity and scope of the biomedical sciences are advancing rapidly. FDA is under constant threat of falling behind innovators and inventors, who develop products submitted for approval to FDA – one of many critical issues brought to the attention of the public and Congress in the 2007 report *FDA Science and Mission at Risk* (*"Mission at Risk"*).

In 2013, the Commissioner of Food and Drugs requested that the FDA Science Board again consider the state of the Agency's science and review FDA's progress since 2007. Specifically, the Science Looking Forward Subcommittee was created to evaluate three principal areas within the Agency: 1) Priorities and emerging needs; 2) extramural programs and collaborations; and 3) supporting an environment of scientific excellence.

Accordingly, as noted in this report, the Subcommittee has identified progress made to strengthen FDA's scientific capacity in response to the 2007 report, summarized the challenges that FDA faces in the coming years, and made recommendations on how the Agency can continue to build on its past progress.

This report is based on the review of extensive data and information requested by the Subcommittee and provided by FDA staff[10]; presentations requested by and made to the Subcommittee by FDA leadership and staff; and review of other relevant materials, including other related reports and publications.

[9] And, of course, many other countries look to or rely upon FDA decisions, especially in the approval of new medical therapies.
[10] See Appendix A.

Area I: Priorities and Emerging Needs

Introduction

The Subcommittee was asked to consider a series of questions in relation to priorities and emerging needs, especially about whether and how FDA can meet the future challenges of technological advances in areas including, but not limited to, medical product development, food safety, and advanced product manufacturing. These questions were specifically:

a. In addition to FDA's responses to the 2007 *Mission at Risk* report, are there further measures and actions the Subcommittee would suggest to continue to improve coordination, maximize use of existing resources, and advance regulatory science capacity at FDA, and are there specific areas where targeted change or investments would increase the impact of changes already implemented?

b. With respect to the *Strategic Plan for Regulatory Science,* which FDA issued in 2011, does the Subcommittee concur with the strategic priorities FDA has articulated, or are there any that need to be added or eliminated to meet current and future needs, given the rapidly changing scientific landscape? If modifications are required, what changes should be considered, and should equal weight be given to each of the priority areas?

c. Are there areas of emerging science that FDA will need to address that have been overlooked? What factors should be considered when prioritizing how to address emerging areas of science that affect FDA's regulatory and public health mission?

Progress Made Since the 2007 *FDA Mission at Risk* Report

The Subcommittee is impressed by the many positive responses FDA made to the 2007 report. It also observes that questions about FDA's competence that were being asked frequently at the time of the *Mission at Risk* report have receded. One small example of this is that published commentaries that used to raise questions about drug safety now admire FDA for "exploring radical new approaches for…genomic testing."[11]

However, FDA's mission now appears to be at risk due to an expanding and extraordinary range of increasingly complex responsibilities and insufficient resources with which to address them. Organization and efficiency can only do so much to address the regulatory issues related to the advent of such challenges as stem cells, engineered tissues, gene therapies, omics, genomic modification, Ebola, the resurgence of pertussis, the microbiome, food safety, robotics, software as medical devices, security and privacy of software in medical devices, 3D printing, whole-genome sequencing, and personalized medicine.

[11] Lander ES. Cutting the Gordian helix-regulating genomic testing in the era of precision medicine. N Eng J Med, 2015;372:1185-6.

While a list of organizational and programmatic changes FDA has made since 2007 to contribute to its improved capabilities is too lengthy for a comprehensive accounting, the most important are:

- The establishment of new offices/organizations within FDA. The creation of an Office of the Chief Scientist now helps to ensure better coordination and promotion of the Agency's science. These changes also include new offices focused on supporting regulatory science, the professional development of Agency scientists, health informatics, scientific integrity, minority health, and a group devoted specifically to medical countermeasures for acts of terrorism and emerging threats.
- The *Senior Science Council* gives program directors a forum for developing over-arching regulatory science priorities, devising policy, and coordinating scientific issues across the Agency. A new Office of Foods and Veterinary Medicine was created to lead a functionally unified foods and veterinary medicine program and enhance FDA's ability to meet today's great challenges and opportunities in food and feed safety, veterinary medicine, nutrition, and other critical areas.
- The Center for Tobacco Products was established to oversee FDA's regulatory authorities over the manufacture, marketing, and distribution of tobacco products.
- New statutory authority from Congress that not only improves FDA's ability to tackle public health problems but also increases the Agency's responsibilities. These new authorities include (a) regulatory authority over cigarettes and other tobacco products; (b) modernizing FDA's approach to overseeing food safety, including a greater reliance on preventive controls and science-based standards, new enforcement authorities, and better oversight of imported foods; (c) new authorities to expedite the review of generic drugs and to better protect imported drugs; and (d) a new regulatory paradigm for drugs manufactured ("compounded") by pharmacies and for the market entry of "biosimilar" drugs. In addition, (e) new offices FDA established in China and India to strengthen oversight of imported products.
- The publication of scientific rationale for many key decisions by FDA scientists and leaders, improving the ability of the public and other stakeholders to understand the processes and limitations under which FDA operates.
- Initiatives across FDA programs to deal with important new and emerging technologies, such as stem cells, 3D printing, predictive toxicology, genome sequencing and computer simulation.
- A Precision Medicine Initiative, in coordination with the National Institutes of Health (NIH), that aims to revolutionize medicine by developing new therapies based on the genetic makeup of patients.
- Advances in regulatory science that enhance the implementation of the lifecycle approach to regulation for the approvals of drugs and devices and to the ongoing evaluation of their benefit-risk profile in the postmarket setting.

- Increased funding, from both appropriations by Congress and user fees paid by industry activities, which has enabled FDA to increase its capabilities in several areas (although significant deficits remain in others); and additional funding for FDA to substantially meet an almost half-century-long goal of acquiring a centralized campus with state-of-the-art laboratories (such as the Life Sciences Biodefense Laboratory that opened in 2014).
- Increased focus on postmarket surveillance, primarily in the form of the Sentinel Initiative active surveillance system, which draws on existing health care data (such as reimbursement claims) to continuously monitor the safety of medical products. Also, FDA launched the unique device identifier (UDI), which will become a crucial element in the success of postmarket surveillance systems for medical devices.
- Advances in regulatory science and publication of findings. For instance, in one recent article that reviewed 302 new drug applications submitted between 2000 and 2012, about half were approved on their first submission. FDA scientists identified preventable deficiencies in drug doses and study endpoints that led to delayed or denied approval.[12] The article notes that, "Early and frequent dialogue between the FDA and drug sponsors" has the capacity to accelerate approvals without diminishing the level of evidence required for approvals.

Challenges and Recommendations

FDA noted for the Subcommittee that scientific advances are occurring rapidly across all areas of the Agency's purview, which will profoundly affect whether FDA can adequately protect the public and support innovation in new product development. The Subcommittee agrees with FDA's conclusion that the future holds formidable challenges.

Assuming FDA can appropriately incorporate these advances into its regulatory mechanisms, their value to public health and medical innovation cannot be overestimated. Congress, the Administration, industry stakeholders, and patient groups are focused on identifying ways in which FDA's processes for evaluating new medical products can be improved and expedited.

Development of a new pharmaceutical therapy can take up to a decade and cost hundreds of millions, even billions, of dollars, and future discoveries could be even more complex. Many new therapies will result from combinations of pharmaceuticals and medical devices; others will result from sequencing of human genomes. Yet others might require that FDA approve them using new "predictive" techniques for clinical evaluation that are not fully developed (such as Bayesian statistics and "Big Data") yet.
Thus, the Subcommittee recommends that FDA give priority to the following:

[12] Sacks LV, et al. Scientific and Regulatory Reasons for Delay and Denial of FDA Approval of Initial Applications for New Drugs, 2000-2012. JAMA, 2014; 311: 378-84. Available at: http://jama.jamanetwork.com/article.aspx?articleid=1817795. Accessed on Sept. 9, 2015.

Medical Product Innovation

Background

The Subcommittee notes that improvements in the review of new medical products have been steady and impressive. FDA reports that it has led the European Union and other advanced regulatory authorities every year in the introduction of novel (new molecular entity) drugs; and that nearly two-thirds of significant new pharmaceutical advances that were approved anywhere in the world in 2014 were approved first by FDA, further cementing U.S. leadership in biomedical innovation.[13]

Similar, albeit less dramatic, progress has been made in the review of medical devices. Not only has that resulted in faster access for patients to life-saving new therapies, it has encouraged investment in the biomedical sciences, which will, in turn, result in yet more innovation in the therapies of the future.[14] With efforts to accelerate approvals, it is important that postmarket studies provide necessary information about the benefit-risk profile of drugs, devices, and biologics during their entire lifecycle.

The Subcommittee feels strongly that FDA should continue to promote novel regulatory science efforts that advance the lifecycle approach to regulation during the entire market life of drugs, devices and biologics. However, the biomedical industry, academia, and patient groups have expressed concern about the ability of current FDA resources to continue supporting innovation and the lifecycle approach in so many domains.[15] The Subcommittee agrees with those concerns, and offers the following recommendations to support and stimulate biomedical innovation:

Recommendations

1. Facilitate the qualification of biomarkers, including surrogate endpoints, where appropriate, for the evaluation of new therapies, especially for conditions that have no effective treatments, such as Alzheimer's. Encourage additional research on new biomarkers to ensure their clinical validity and work on providing guidance on how new biomarkers can be qualified as surrogate endpoints.
2. Encourage and facilitate the development of clinical trial networks and "master protocols," especially in the areas of oncology and antimicrobial therapy, to expedite clinical trials and reduce their costs. The current process of designing a new clinical trial for every new product – at great cost in time and resources – should, where practical, be replaced by the

[13] Novel New Drugs 2014 Summary. Available at: http://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/DrugInnovation/UCM430299.pdf. Accessed on Sept. 14, 2015.

[14] In January 2015, the National Venture Capital Association reported that "Biotechnology investment dollars rose 29 percent in 2014 to $6.0 billion . . , placing it as the second largest investment sector for the year in terms of dollars invested."

[15] See, for example, "Advocates say 1% funding increase in proposed US budget would 'weaken' FDA, "March 6, 2014, Friends of Cancer Research; and Phrma statement on FDA's 2016 budget, February 2, 2015

use of trial networks and master protocols. FDA should provide technical assistance and regulatory advice to developers of "master protocols."

3. Expand the use of "Bayesian" designs and "adaptive" methods in clinical trial development, which allow developers of medical products to build more flexible clinical trials and thus improve the chances of obtaining dispositive data for a new product approval.
4. Expand the Sentinel Initiative to provide "real-time" safety data and to evaluate the effects of major safety warnings or label changes on the use of drugs in the population; enhance and expand national medical device surveillance efforts by leveraging Sentinel and using unique device identifiers.
5. Establish obtaining ongoing access to external experts in emerging technologies to help accelerate approvals, before Advisory Committee meetings.
6. Evaluate, use, and perform risk-based safety assessments of emerging technologies, such as nanotechnology, which could benefit public health and regulatory science.

Food Safety and Applied Nutrition

Background

FDA is responsible for ensuring that the food supply is safe, sanitary, wholesome, and honestly labeled. The composition of the American food supply, however, is constantly changing with shifting consumer preferences, the identification of new food contaminants, the introduction of new food additives and technologies, the proliferation of dietary supplement products, and the continuing growth of imported foods.

FDA has little or no pre-market oversight of such changes and must rely on postmarket oversight to understand their impact on the nutritional quality and safety of the food supply. Moreover, FDA has historically lacked basic information and analytical tools that are essential for food oversight.

The passage of the Food Safety Modernization Act (FSMA) in 2010 modernized food safety oversight by mandating a new approach that incorporates modern scientific principles and risk analysis. The Science Board has been told that its strong statement in 2007 about the state of food safety oversight was a valuable addition to the calls by industry and consumers for Congress to enact FSMA.

Not surprisingly, implementing FSMA has been a challenge: Congress has thus far provided only a fraction of the needed resources. For example, of the approximately 133,000 international food producers, the FDA currently has resources to inspect only about 1,000 per year;[16] the

[16] FSMA Report to Congress, Department of Health and Human Services, May 2013. As of June 2015, FDA registered 133,000 foreign facilities and 97,000 domestic, for a total of 230,000 food manufacturing sites (source: FDA/CFSAN Food Registration Program)

Congressional Budget Office has estimated that FDA will need almost $600 million in additional funding to accomplish this daunting task.[17]

The President requested an increase in food safety funding of about $110 million for fiscal year 2016, but it appears that Congress is poised to provide only about a quarter of that amount. Significant data gaps impede FDA's ability to effectively implement the risk-based approach mandated by FSMA. For example, due to the lack of scientific data, FDA has deferred making decisions about the application of untreated biological soil amendments of animal origin, including raw manure, to grow crops.

Similarly, there are important epidemiologic data gaps that affect the burden of disease estimates and attribution models that serve as the foundation for FSMA's risk-based framework. Given these challenges, the Subcommittee is concerned that, without sufficient resources, FSMA will represent a missed opportunity to create a modern, prevention-based food safety system in the United States.

In addition to food safety, FDA is also charged with the oversight of nutrition labeling, dietary supplements, and cosmetics. The area of nutrition is one of FDA's weakest, receiving only 1% of the agency's food funding and a far smaller portion of FDA's overall budget; thus, the agency faces significant challenges to perform basic functions that fall within its statutory mandate. Increasing FDA's ability to address important nutrition issues would contribute to significant gains in public health – around 400,000 deaths in the U.S. each year are attributed to poor diet and inactivity.[18] Specifically, 37% of adults have cardiovascular disease, 34% have hypertension, 11% are diabetic, and over two-thirds are overweight or obese.[19] About a third of children are overweight or obese, and onset of type 2 diabetes, once known as adult onset diabetes, now occurs during childhood.[20]

With respect to FDA's oversight of the $35 billion dietary supplement industry, the Subcommittee has not examined that program in detail, but understands that FDA is undertaking a review of its authorities and limitations in ensuring the safety of those products. The Subcommittee recognizes the difficulties in regulating a large industry with so little authority and resources, and commends FDA for considering any strategy changes that might be possible for better protecting the public from unsafe dietary supplements.

The Subcommittee continues to be concerned about the state of food (and cosmetic)[21] oversight at FDA and offers the following recommendations to improve FDA's ability to meet the food challenges of the 21st century:

[17] CBO Report on S.10, Food Safety Modernization Act, August 12, 2010

[18] Mokdad AH, Remington PL. Measuring health behaviors in populations. Prev Chronic Dis 2010;7(4):A75. Available at: http://www.cdc.gov/pcd/issues/2010/jul/10_0010.htm. Accessed 7/16/15

[19] Ibid

[20] *Accelerating Progress in Obesity Prevention: Solving the Weight of the Nation*, Institute of Medicine, May 8, 2012.

[21] Consumer and industry groups have proposed new legislation to address perceived safety gaps in cosmetics that would enhance FDA's ability to oversee cosmetic ingredient safety.

Recommendations

1. Adjust the definition of regulatory science to be more inclusive of food safety, veterinary medicine, and nutrition.
2. As FSMA rules are implemented, use regulatory science approaches to:
    a. enhance risk analytics to target resources most effectively;
    b. develop risk mitigation strategies or preventive controls through targeted research; and
    c. develop outreach and risk communication strategies aimed at producers, retailers and consumers.
3. Help people improve their diets and reduce the toll of chronic, diet-related disease by enhancing resources in the behavioral sciences, expanding FDA's under-resourced nutrition initiatives, adopting the latest scientific procedures to understand how consumers read food labels and menus and can best be influenced by nutrition information, and fostering calorie information on menus.
4. Enhance initiatives to improve:
    a. monitoring of the consumer exposure to food components and contaminants, including tracking exposures over time
    b. screening methods for detecting chemical and microbiological contaminants in food, and animal feed and
    c. integrating and applying modern toxicology to predict risk of such contaminants.
5. Increase the use of statistically relevant sampling schemes for improved analytical results.
6. Develop tools that are essential for monitoring and evaluating changes in various food components (e.g., food additives, compounds found in food packaging, pesticides, heavy metals, bioactive substances, and nutrients).
7. Collaborate with CDC to modernize public health surveillance of foodborne diseases to keep pace with new methodologies and technologies, including culture-independent diagnostic tests (CIDTs).
8. Work with other agencies (e.g., NIH, NSF, USDA) to ensure that regulatory science research needs around food are being adequately funded.
9. Explore mechanisms for leveraging public and private sector data sources to inform food safety risk analysis.
10. Develop expertise in parasitic and fungal foodborne pathogens.
11. Elevate the status of the dietary supplement program within the larger foods program and consider how dietary supplements oversight can be increased and strengthened.

Product Manufacturing and Quality

Background

FDA notes that continual advances in science and technology drive the development of new FDA-regulated products and lead to paradigm shifts in manufacturing techniques. The manufacturing of medical products is undergoing a sea change in both processes and the use of new technologies. Products are increasingly being made using nanotechnology; human stem cells are being harvested to create new therapeutics; robots and 3-D printing are being used to make complicated medical devices; and manufacturers are making "biosimilar" versions of complex proteins that are viewed by the public as cost-saving "generic" biologics.

To effectively evaluate product quality and safety, FDA and industry need advances in scientific and technical capabilities as well as new tools to: fully characterize products and processes; identify and monitor attributes critical for their appropriate intended use; and understand the impact of new manufacturing methods on product quality and safety. The Subcommittee believes the following recommendations, if adopted, would greatly improve FDA's ability to ensure manufacturing quality in the future:

Recommendations

1. Expand use of the latest DNA technology to characterize medical products, including vaccines, and to ensure their purity and safety. Also, expand use of the latest DNA technology to identify the source of foodborne disease outbreaks. FDA has begun to use "next generation" sequencing data, which can generate massive amounts of DNA data in much less time and at less cost than earlier methods. Increasing use of CIDTs in clinical settings will greatly improve the ability of physicians to diagnose and treat patients with foodborne illness but, at the same time, threatens the current foodborne disease surveillance system, which relies on isolates obtained from traditional culture-based diagnostic methods. FDA will have to weigh these trade-offs as it considers new CIDTs for approval and work with CDC to ensure that the surveillance infrastructure for foodborne diseases keeps pace with new technologies
2. Expand the use of appropriate analytic methods for assessing purity of products made using nanotechnology, to ensure that products of nanotechnology are being safely handled in the laboratory and introduced into food, cosmetics, and medical products.
3. Prepare to evaluate the production of "biosimilar" drugs by using the latest high-resolution analytic methods to identify structural and functional determinants of recombinant therapeutic proteins.
4. Equip field staff with novel technologies, such as hand-held monitors that use Raman spectroscopy, to screen imports for evidence of contamination or counterfeiting. This will improve safety protections for imported foods, drugs, and other products.
5. Use new technologies such as next-generation sequencing, bioinformatics, resistomics, transcriptomics, metagenomics, and metabolomics to monitor trends and mechanisms of antibiotic resistance.

Modernizing Toxicology

Background

Across most of FDA's programs, toxicology is critical to the Agency's ability to predict product safety or assess the significance of chemicals used in foods, pharmaceuticals, vaccines and other FDA-regulated products. Much of FDA's toxicology effort today is derived from decades-old principles and based on the use of laboratory animals to extrapolate to human experience.

Recent advances in the science of toxicology offer opportunities to reduce the use of animals in testing as well as expedite approval of new products for patients. FDA has taken significant steps toward modernizing its toxicology programs, such as an increased focus by the Chief Scientist, enhanced training of staff, grants for toxicology research, and partnerships with external groups (e.g., NIH) to explore new testing approaches. But the Subcommittee concludes that much work remains to be done and that opportunities abound:

Recommendations

Adopt the latest technologies to help identify and qualify biomarkers of toxicity, including:

1. Induced pluripotent stem cells to produce cell types for evaluation of toxicity
2. Bioimaging coupled with cognitive and functional testing to help determine neurotoxicity
3. Mathematical modeling of cells and physiological systems
4. Improved methods of *in silico* modeling to identify patient-specific susceptibilities to individual drugs
5. Organ-on-a-chip technology to study toxicities, such as drug-induced pancreatitis

Leadership and Coordination

Background

The Subcommittee reiterates that the evolution of science is constant, and that FDA will need to address future scientific advances in many areas, including next-generation diagnostics, platform-based solutions to multiple diseases, and emerging regulatory issues such as e-cigarettes and state legalization of recreational pharmacologically active substances.

Since the future can be predicted only as it comes into view, the Subcommittee believes FDA needs to be proactive in developing a method to continuously scan the horizon for future challenges and opportunities. This might best be accomplished by using the skills and expertise of a select group of experts who are best positioned to know of new technologies and approaches as they come into being.

For example, technology is becoming available that will allow FDA to significantly expand its capacity to conduct surveillance of products on the market. "Big Data" from health care providers, industry, insurers, and other government agencies will give FDA vast new data sources to not only conduct continuous safety monitoring of such products but to mine the vast

amount of data in the public domain to identify and prioritize emerging technologies and scientific advances across all areas.[22]

Recommendations

The Subcommittee recommends that:

1. FDA request new funding for the Office of the Chief Scientist to:
    a. provide the necessary infrastructure to coordinate the allocation of core scientific capabilities and resources within and across the Centers, based on current and future priorities
    b. modernize toxicology and bioinformatics and
    c. proactively establish collaborative programs with other government agencies and other partners.
2. FDA amend the Science Board charter to:
    a. ensure more continued engagement of the Science Board in identifying promising new scientific opportunities and challenges;
    b. enable the Science Board to make recommendations to FDA about future priorities and possible collaborations and
    c. include representation from other Federal partners.

Area II: Extramural Programs and Collaboration

Introduction

The importance of enhancing an organization's breadth, depth, and scope by tapping expertise and perspectives outside its own internal environment cannot be underestimated. Scientific discoveries and advances are occurring at dizzying rates and innovation and action require input from multiple sectors. Indeed, successful collaborations leverage human, financial, and scientific resources to attain ambitious common goals with precision, competence, and speed.

Collaboration is a cornerstone of FDA's efforts to help drive innovation in product development. As a regulatory agency, its role in the innovation process is to promote the most efficient regulatory pathway for product approval and market release, while ensuring that new diagnostic and preventive tools, treatments, and cures are safe and effective for human and veterinary use.

Furthermore, FDA also protects the public health by ensuring that accurate, science-based information is available for the safe use of medicines and foods, regulation of tobacco products, and to proactively combat terrorism threats.

[22] Blog by FDA IT Director, http://blogs.fda.gov/fdavoice/index.php/2014/06/fda-leverages-big-data-via-cloud-computing, June 19, 2014

Globalization, rapidly evolving technologies, and emerging areas of science are having a major impact on FDA-regulated products and FDA's role in protecting public health. Leveraging the knowledge gained from them to create novel tools and processes needed for 21st-century product development and oversight is too vast and complex a task to be done by any one organization. It requires the close collaboration of all stakeholders—Federal agencies, industry, researchers, patient/consumer groups, health care practitioners, and others.

The Subcommittee was asked to address what factors should be considered when evaluating the impact of FDA's collaborative activities and how to prioritize extramural programs and partnership opportunities. It began by identifying and describing the progress made in this area in recent years.

Progress Made Since the 2007 *Mission at Risk* Report

Following the 2007 report, FDA established intra-Agency initiatives and extramural programs and partnerships designed to meet the Agency's regulatory science needs. These activities enable key components of the Agency's vision for advancing regulatory science, released in a 2010 white paper titled *Advancing Regulatory Science for Public Health.*[23] Furthermore, extramural programs and collaborations are also required to meet the eight scientific priorities identified in the *Strategic Plan for Advancing Regulatory Science at FDA*[24] in 2011 and the ninth priority area, *Strengthening the Global Product Safety Net*, added in 2013.

These programs and collaborations are enabled by vehicles such as the Centers of Excellence in Regulatory Science and Innovation (CERSIs) and the Broad Agency Announcement (BAA), established in 2011 and 2012, respectively, through well-established mechanisms such as grants, contracts, and Cooperative Research and Development Agreements (CRADAs), and by the formation of unique public–private partnerships and consortia. In this context, the Subcommittee was asked to comment on the external stakeholder's view of the value of these programs to fulfill FDA's regulatory mission.

Scientific partnerships have been developed with other Federal agencies, with state and local governments, with academia, and the private sector, as well as with international agencies and governments to build a global regulatory science capacity. More specifically, FDA has built robust collaborations to tackle the widening gap between advances in basic science and their application to the development of new treatments, diagnostics, and vaccines in a wide variety of applications, including for human health, veterinary uses, food technology, and tobacco products.

Examples are presented in Appendix B. Some noteworthy partnerships demonstrate innovation and success in this area, and are described more fully in the appendix:

[23] Advancing Regulatory Science for Public Health report
[24] Strategic Plan for Advancing Regulatory Science at FDA

- The Common Electronic Submissions Gateway with Health Canada has allowed Canada to share FDA electronic submissions used for new drug reviews and will likely be the beginning of a permanent mechanism for greater regulatory cooperation between the two nations.

- The Musculoskeletal Atlas Project, a joint effort with the University of Auckland (New Zealand), will generate accurate computational models of the human skeleton that are expected to help speed the design, development, and testing of new orthopedic medical devices.

- The Western Center for Food Safety (WCFS) is a Center of Excellence that was established in 2008 by a cooperative agreement with the Western Institute for Food Safety and Security at the University of California, Davis. WCFS research, outreach and education programs enhance the FDA's implementation of the prevention-oriented activities outlined in the Food Safety Modernization Act.

- A CERSI at the University of Maryland focuses on modernizing and improving the ways drugs and medical devices are reviewed and evaluated.

- The Medical Device Innovation Consortium (MDIC) is a not-for-profit public-private partnership that combines industry, government and patient organizations to improve the medical technology environment and advance medical device regulatory science, which is in turn expected to speed the development of new medical devices, lower the costs of their development, and raise the overall quality of devices produced in the United States.

- FDA's National Center for Toxicological Research, in Arkansas, established a Center of Excellence for Regulatory Science with the state of Arkansas that will leverage intellectual, human and financial resources among Arkansas academic institutions to further FDA's regulatory science efforts.

- The Population Assessment of Tobacco and Health (PATH) Study, established with NIH via a contract with Westat is a nationally representative, longitudinal cohort study of approximately 46,000 never, current, and former users of tobacco products in the United States that will inform CTP's tobacco regulatory activities.

- In collaboration with NIH, FDA established the Tobacco Centers of Regulatory Science (TCORS) to conduct cutting-edge research related to the regulation of tobacco products research in September 2013.

Challenges

Since the issuance of the 2007 report, FDA has made increasing use of the types of collaborative mechanisms described above. In doing so, FDA has acquired knowledge and experience in the conception, establishment, and nurturing of these partnerships and collaborations. Although individual goals, scope, and timeframes differ, this group of FDA programs and projects generally share important common features. For example:

- They are constituted by stakeholders whose individual contributions and aligned common interests synergistically contribute to the success of the enterprise
- The projects support mission-critical scientific research
- Each has clearly defined governance and management structures and
- Access to data and publication policies are established at the outset.

FDA is well positioned to forge collaborations in the precompetitive space and to identify scientific hurdles in regulating new products. An important outcome, especially in a time of resource constraints, is that these activities increase and facilitate communication among stakeholders, creating greater efficiencies for the particular project at hand and beyond. The experience of the past few years has taught us that successful partnerships, collaborations and alliances require:

- Shared vision;
- Active involvement of all members;
- Crisp, attainable goals and objectives that are of value to the various parties;
- A dedicated team of highly qualified professionals who have the necessary expertise;
- Clear roles and responsibilities;
- Innovative mechanisms to leverage and pool energy, ideas and resources;
- Supple infrastructure to deliver solutions required by multiple partners;
- Respect for core principles of inclusion, openness, transparency, and ethical behavior.

FDA's ability to create such partnerships, however, is limited by the rules and regulations that apply to Federal agencies. These inherent constraints are compounded by FDA's necessary sensitivity to real or perceived conflict of interest (COI) that arises from its regulatory role.

Finding and implementing mechanisms that can surmount such strict hurdles narrows the FDA's degrees of freedom and nimbleness. Therefore, it is particularly laudable that FDA has successfully and creatively catalyzed critically important scientific activities using traditional mechanisms, such as CRADAs, and novel authorities, such as those granted by the FDA Amendment Act (FDAAA) passed in 2007, authorizing FDA to engage in Public-Private Partnerships (PPPs).

Recommendations

Despite the barriers described above, the Subcommittee believes that continued – indeed, expanded – partnerships and collaborations will be imperative for FDA to pursue if the Agency is to stay current with the rapidly advancing science on which it depends, while most efficiently using its resources to leverage the substantial external expertise available to it through such collaborations.

The Subcommittee thus urges FDA to consider the Reagan-Udall Foundation (RUF) an essential part of its regulatory science mission and to use it in a broader array of areas. Some examples might include: expanded research in new approaches in predictive toxicology; ascertaining the use and value of CERSIs; spurring the professional development of researchers interested in regulatory science; and further creating research communities that can serve as public-private partnerships.

Established by FDAAA in 2007 in response to the *Mission at Risk* report,[25] RUF is designed to catalyze programs and projects by bringing relevant parties to the table (FDA, patient/consumer groups, academia, other government entities, and industry) to work together transparently to create pivotal new regulatory science.

As well as being authorized to create public-private partnerships, the RUF's statute also grants it authority to raise funds, including from foreign entities, an important factor as prospects diminish for Federal funding of research. Because RUF works outside the regulatory space, it can support FDA's scientific mission and help FDA achieve its goals in new and nimble ways. For example, FDA can leverage RUF's capability of running projects whose outcome the Agency will one day regulate, without running into a conflict of interest.

The broad scope of the regulatory science enterprise and the range of disciplines and skills it must call on to deliver on the promise of the new science are often poorly understood. Specifically, the need for data required for regulatory decisions – those that allow FDA to determine, for example, if a potential new drug, a novel vaccine or an imported food is safe for people – is inadequately matched by the Agency's limited resources. The Subcommittee appreciates the value of RUF in helping solve this quandary, and foresees ever greater value that can be derived from expanded use of RUF.

With very limited resources available for research that informs the regulatory process, it is imperative that FDA maximize available funds, leverage its investment, and attract new resources. Even as it does so, without increased appropriations, the United States is condemned to sluggish development of regulatory science and an Agency that cannot possibly keep up with scientific advances. The Subcommittee's recommendations in this area are summarized below:

[25] See Appendix C.

1. Enhance funding.
    a. Realistically ascertain the level of financial resources required for successful partnerships and collaborations, and ensure that projects have the means to succeed, either directly from FDA's existing budget, by requesting new funds or by leveraging resources from other stakeholders, including the RUF.
2. Catalyze novel extramural partnerships that support and enhance the Agency's mission.
    a. Work with RUF to expand FDA's range of activities and obtain additional resources
    b. Partner more aggressively with research universities and institutes to take advantage of faculty teams and centers already focused on FDA-related areas of study
    c. Seek collaborations with research supporting foundations to extend the Agency's research agenda and needs.
3. Establish a portfolio approach to extramural collaborative alliances.
    a. Set priority areas/topics and match collaborative projects to strategic goals at the Center, Office, and Agency levels
    b. Pinpoint existing scientific, technical or knowledge gaps that need to be addressed
    c. Consider the needs of the FDA community and its constituents
    d. Identify key players, champions and decision makers
    e. Use appropriate project mechanisms (RUF, BAA, etc.) for implementation
    f. Review the portfolio systematically for balance and impact (scientific area, maturity, purpose, risk/rewards, etc.)
    g. Weed out obsolete projects after considering input from internal and external stakeholders.
4. Mobilize other resources.
    a. Ensure recruitment and retention of highly qualified staff and enable their interactions with academia and private sector scientists
    b. Use the framework of FDA's Technology Transfer Program to develop successful partnerships and collaborations with external organizations, including but not limited to, CRADAs, licenses, material transfer agreements, etc.
    c. Facilitate access to information, data, intellectual property, materials, etc., through partnerships and collaborations.
5. Address structural hurdles, i.e., legislative, policy, authority, conflict of interest.
    a. Identify internal policies or procedures that curtail FDA's ability to expand its scientific reach through collaborative programs
    b. Develop appropriate legislative strategy to address barriers
    c. Educate stakeholders on FDA's capabilities and partnership opportunities.

Area III: Supporting an Environment of Scientific Excellence

Introduction

As a scientific regulatory agency, FDA must recruit staff with a range of scientific credentials, including physicians, toxicologists, pharmacologists, microbiologists, biomedical engineers, and many other highly skilled professionals. The normal pay scale for Federal employees is known as the General Schedule, with pay grades from GS-1 to GS-15.

A few senior managers are promoted into the Senior Executive Service, which has somewhat higher pay. Congress has given some agencies with special hiring needs such as NIH and FDA special, higher pay authorities, including Title 38 (for physicians, dentists and nurses), Title 42 (for scientific experts), and the Senior Biomedical Research Service (in FDA, for the most outstanding research and review scientists). But FDA has been restricted in its use of those pay authorities, to the detriment of the Agency's ability to ensure scientific excellence, as discussed below.

Progress Made Since the 2007 *Mission at Risk Report*

FDA has taken several actions in recent years to foster an environment of scientific excellence. For example, the Agency created an organization specifically devoted to scientific professional development within the Office of the Chief Scientist that has created a host of new recruitment, fellowship, and training programs for Agency scientists. Nonetheless, the Subcommittee has found that basic problems with staff recruitment and retention have not been addressed – these must be dealt with to further support a culture of scientific excellence and creativity. These problems arise from limitations in salaries and other benefit issues for FDA personnel.

Challenges

The pay and award concerns identified by the Subcommittee can be summarized into four categories:

1. **Salaries** - FDA must recruit scientists from medical schools/academia, industry, and other sectors that generally pay their employees more generously than government. FDA managers have numerous examples of recruitment efforts that are thwarted by pay limitations. For example, a well-paid private-sector physician might be willing to take a 50% pay cut to do public service, but FDA can pay them only 25% of their current pay, and they cannot afford to live in the Washington, D.C. area for such reduced pay. FDA has attempted to use the "expert" pay authority embodied in Title 42 of the Public Service Act to recruit more such experts, but officials in the Department of Health and Human Services have restricted use of Title 42, thus limiting a valuable recruitment tool that FDA could use effectively. The net result is that many eligible and desirable candidates for scientific positions at FDA simply do not apply and are not motivated to take the financial loss for equally demanding

work. The opportunity cost to the Agency is difficult to measure, but is judged by this Subcommittee to be significant.

2. **Bonuses and merit increases** – FDA has no mechanism to give outstanding scientists meaningful bonuses or merit increases in their salaries. Indeed, even the modest bonuses that were allowed have been restricted, reportedly due to adverse publicity regarding Federal benefits during a weak economy. Even when permitted, annual performance awards and merit increases are not competitive with the private sector nor do they award exceptionally high performers appropriately.[26]
3. **Continuing education** - Rapid advances in omics, informatics, and health IT require that intramural staff update their skills and stay abreast of the science, which frequently requires significant investments of time and effort. Continuing education as well as presentation of one's research in scientific conferences is important to maintaining the knowledge, competencies, and skills of science personnel in any organization as well as ensuring that the work product of scientists -- from research to product reviews -- is informed by the current state of the art in their specific scientific fields.

   However, the recent and current Federal policies on attending such conferences or other education venues have severely limited FDA's ability to access continuing education, reportedly due to a small number of unrelated, visible travel abuses in other Federal agencies.
4. **Conflict-of-interest restrictions** - The ability to pay at market rates to prospective employees is further complicated by convoluted Federal government ethics regulations.[27] The result is that prospective extramural talent is subjected to extensive, and appropriate, review of their financial holdings with the real possibility of facing divestiture no matter the relevance of a particular financial investment.

In addition to the basic concerns described above, the mechanisms by which the FDA budget request is generated, appropriated, and managed during the post-appropriation period is opaque to Center Directors and line managers and further impedes FDA's ability to recruit scientific talent. There are major oscillations in the monies available for continuing professional education, retention and recruitment activities – let alone programmatic priorities. At a time when private industry and academia are making multi-year budgetary plans and commitments for *big data, data science, informatics, pharmacovigilance* and other scientific initiatives, these financial fluctuations create instability in the Agency's scientific programs, morale, and the attractiveness of intramural programs to prospective recruits. Such uncertainty in the future of programs and initiatives likely contributes to the reluctance of potential recruits to engage with the FDA.

[26] The current annual merit-based reward strategy appears to be based on a principle of equality across the Agency without paying attention to the reward of outstanding scientific excellence.
[27] Available at: http://www.fda.gov/AboutFDA/WorkingatFDA/Ethics/ucm079670.htm. Accessed on Sept. 9, 2015.

Coupled with seemingly archaic HR and ethics processes, there is general uncertainty about the reasons for protracted administrative procedures that cause delays in purchasing, awarding of travel privileges, and recruitment. The resulting malaise stifles creativity, innovation, and entrepreneurial activities that advance FDA's mission and its ability to be nimble in response to the challenges of rapidly evolving technologies, science, and regulatory science. While there is a public policy driver for sure-footedness in a rapidly changing and turbulent scientific field, FDA will need to be more flexible and forward looking in its management as it successfully protects the health of the public.

Recommendations

1. Revise human resources and ethics processes to increase flexibility in recruitment, retention, purchasing, and awarding of travel privileges. Current, outmoded HR and ethics processes result in malaise that stifles creativity, innovation, and entrepreneurial activities that advance the agency's mission.
2. Take full and expanded advantage of Title 38 and 42 in the hiring process, within limitations of the law.
3. Expand retention pay for hard-to-recruit specialists, such as specialty physicians, biomedical engineers, quantitative methodologists, and biostatisticians, toxicologists, and other hard-to-recruit specialists.
4. Seek "Direct Hire Authority" for scientific staff for at least five years, so that FDA can more efficiently fill current vacancies and maximize its public health impact.
5. Seek authority to offer special pay levels, up to that of the President, to outstanding scientists whom the Agency cannot now recruit, or has trouble retaining, due to restrictions on Federal pay.
6. Review the salary structure in view of Federal guidelines and COI rules. Make annual merit awards competitive with those in the private sector and provide increased awards for strong performers.
7. Investigate more nuanced approaches to the assessment of "conflicts of interest" while protecting the Agency's reputation, independence, and integrity and maintaining the public trust.
8. More actively manage and balance the continuing professional education needs of staff, especially those with review responsibilities and deadlines. This includes:
    a. Encourage and pay for increased FDA employee participation (with presentation of their work as appropriate), including that of field employees, at professional conferences, including international ones.
    b. Encourage and promote an environment in which scientific discoveries and methodologies are published in peer-reviewed scientific journals.
    c. Continue development of collaborations with academic/research institutions to maintain and increase knowledge and competencies.
    d. Ensure that employees needing professional credentialing are allowed time for CE credits or other required competencies.

Conclusion

The Subcommittee concludes that FDA has made significant strides in strengthening its scientific capabilities in response to the 2007 *Mission at Risk* report. Its drug review program is a global leader in both speed and quality of review, the focus on improving its science infrastructure and advancing regulatory science is to be applauded, and the new food safety legislation promises to bring a new scientific focus to food protection that will greatly reduce foodborne illness.

Nevertheless, medical and technological advances continue at a steady and relentless pace, and the food supply continues to become more global and complex. FDA must stay abreast if it is to remain the pre-eminent consumer protection agency that the public expects. To do that, the Subcommittee urges the Agency's leadership to embrace the findings and recommendations embodied in this report, which are targeted not at changing the organization but on preparing it for the challenges ahead.

The Subcommittee believes that FDA must move quickly to adopt the latest scientific developments in regulatory science as well as ensure that there is no priority higher than the recruitment and retention of its next generation of scientists. Moreover, those responsible for FDA within the executive branch and in Congress must recognize that the Agency cannot carry out the kinds of advances this report has identified without ensuring that it has sufficient authority and resources to do so.

Indeed, FDA is a significant contributor to this nation's leadership in science and in our collective national progress in public health. But, without both the kinds of programmatic improvements we are recommending and the concomitant resources to enable them, the Agency will simply not be able to do its job well. Thus, just as our predecessors found FDA's mission at risk eight years ago, we must reiterate that concern today in light of new challenges and new demands being placed on the Agency, with our hopes that these findings will generate similar public acceptance and support.

Appendix A: Science Moving Forward: A Report to the FDA Science Board

As part of the extensive data and information provided by FDA to the Subcommittee, FDA submitted its report titled, "Science Moving Forward: A Report to the FDA Science Board," which is available at:

http://www.fda.gov/downloads/scienceresearch/aboutscienceresearchatfda/ucm456328.pdf

Appendix B: Noteworthy Examples of FDA's External Collaborations

- The CRADA mechanism – a tried and true way to establish cooperative research projects – was used in an inventive way to create a unique partnership between FDA and Health Canada to create the Commons Electronic Submissions Gateway (CESG). The CESG is one of four initiatives sanctioned by FDA under the umbrella of the Regulatory Cooperation Council that created a new era in a U.S.-Canada regulatory partnership. Specifically, the CESG allows Health Canada access to FDA electronic submissions gateway services; allows the transfer of funds from Health Canada to FDA; respects the legal framework of both parties; enables joint development and customization of the system; and, thus, supports the creation of a permanent mechanism to foster greater regulatory cooperation between the two countries.

- The Musculoskeletal Atlas Project (MAP) resulted from response to a BAA. MAP is a computational model of the anatomy of the human musculoskeletal system. The model can be used to support the development of a range of orthopedic medical devices such as hip implants and total knee replacements.

  A partnership between FDA and the Auckland Bioengineering Institute at the University of Auckland, New Zealand, MAP is part of FDA's effort to advance approaches for developing and evaluating models that better predict patient response. The key deliverable of MAP is an open-source software platform enabling users to rapidly generate accurate computational models of the muscles and bones of the lower body.

  The software architecture leverages several international efforts to develop mathematical models of the human body for clinical, research and educational purposes. It assists the orthopedic research community by enabling rapid generation of accurate musculoskeletal models, facilitating exchange of models and modeling methods, and providing access to unique, comprehensive databases for validation. In the long-term, this database will accelerate the predictive capability of computational models for orthopedic applications.

- The Western Center for Food Safety (WCFS) was established in 2008 by a cooperative agreement with the Western Institute for Food Safety and Security at the University of California, Davis. WCFS research, outreach, and education programs enhance the FDA's implementation of the prevention-oriented activities outlined in the Food Safety Modernization Act. The mission of the Center is to research the interface between production agriculture and food protection, identify real-world solutions to food safety challenges in these systems, and communicate new knowledge through outreach and education. WCSF's current research addresses the development of research approaches and data critical to high priority public health issues addressing FDA regulated fresh fruits, vegetables and tree nuts. Knowledge generated by the WCSF is critical to the development of scientifically validated best practices for mitigating those risks at pre-

and post-harvest production levels. WCSF is enabling research to validate alternative approaches to produce prevention-based controls and provides an understanding of the effectiveness of potential metrics for Good Agricultural Practices.

- CERSIs are critical to FDA efforts to promote faster and better scientific approaches to advancing regulatory science. In the last two years, the University of Maryland CERSI (M-CERSI) held 16 workshops and offered regulatory science lectures. In addition, M-CERSI conducted a series of focus groups to explore patient and prescriber perceptions of patient-prescriber agreements (PPAs, also known as patient prescriber contracts). The study identified several themes concerning the administration, content, effectiveness and usefulness of PPAs. These areas provide a focus for future research to improve PPAs including recommendations for use, patient-centered design of PPAs and burden of compliance on patients and prescribers. The Science Board to the FDA is currently evaluating the CERSI program and should have its findings ready in 2016.

- The Medical Device Innovation Consortium (MDIC) is a public-private partnership devoted to medical product development. It is a not-for-profit 501(c)(3) organization working to improve the medical technology environment and advance medical device regulatory science. Its members include representatives from the medical device industry, patient organizations, not-for-profit groups and Federal agencies including CMS and NIH. The MDIC has developed a framework for incorporating information on patient preferences into benefit-risk assessments of new medical technology and a catalog of methods that can be used to assess patient preferences about the benefits and risks of a medical technology. It works in four areas:

  1) identifying methodology that will raise the overall level of quality of medical devices;
  2) reducing the time and cost required to develop and approve medical innovation, while improving patient safety through the consistent application of validated computational modeling and simulation in device development and regulation;
  3) improving the efficacy and cost-effectiveness of medical device clinical trials;
  4) improving the ability to include patient perspectives in the development, pre-market approval and post-market evaluation of medical devices.

- The National Center for Toxicological Research (NCTR) in Jefferson, Arkansas, the only FDA Center located outside the Washington, DC, metropolitan area, develops innovative tools and strategies, and customizes safety assessments of chemicals and materials in support of the regulatory process focusing on FDA's strategic priorities. NCTR projects involve coordinated expertise from multiple disciplines to maximize the ability to detect adverse outcomes, provide information on the mechanisms underlying toxicity and maximize the ability to translate laboratory findings to the improvement and protection of human health.

In 2011, as part of NCTR's 40th anniversary FDA and the state of Arkansas, through the Governor, signed a first of its kind Memorandum of Understanding (MOU) to establish a virtual Center of Excellence for Regulatory Science, setting the stage for joint research, educational training, collaborations and outreach supporting FDA's mission. A committee, co-chaired by NCTR and the state of Arkansas, includes state government representatives and academic institutions as partners with FDA. The MOU helps FDA leverage intellectual, human and financial resources and further secures the NCTR as one of Arkansas' top research facilities.

- A large scale and critically important research collaboration with NIH is the Population Assessment of Tobacco and Health (PATH) Study. The PATH Study is a nationally representative, longitudinal cohort study of approximately 46,000 never, current, and former users of tobacco products in the United States, civilian, non-institutional population ages 12 and older.

  It is intended to yield comprehensive data on tobacco product use, attitudes, associated health outcomes, and for adults, biomarkers of exposure and tobacco use-related disease processes to inform CTP's regulatory activities. By measuring and accurately reporting on the social, behavioral and health effects associated with tobacco product use in the United States, the PATH study will build on an empirical evidence base to inform the development and assessment of tobacco product regulatory activities by FDA.

- In August 2012, FDA and NIH announced funding to establish Tobacco Centers of Regulatory Science (TCORS). The TCORS program will lead to the creation of a broad coordinated national scientific base of tobacco regulatory research. FDA funded 14 TCORS applications via NIH in September 2013.

  Each center is focusing thematically on areas in which there are significant gaps in knowledge and other critical areas that will contribute to the science base FDA will use to develop meaningful product regulation and inform regulatory activities. The TCORS have the quality and breadth of training necessary to conduct cutting-edge research related to the regulation of tobacco products and play leadership roles in training new researchers in the field.

Appendix C: The Reagan-Udall Foundation

About the Reagan-Udall Foundation

- Independent 501(c)(3) not-for profit created by Congress to advance the mission of the FDA by furthering regulatory science.
- Drives and supports regulatory science research by fostering public-private partnerships and supporting training and scientific fellowships.
- Works with patient/consumer groups, researchers, other government entities and industry.
- Assists in the creation of new, applied scientific knowledge, tools, standards and approaches to evaluate products more effectively, predictably and efficiently.
- Two programs in progress:
    - Development of new tuberculosis drug regimens;
    - Systems toxicology pilot study.
- Developing a fellowship program to bring targeted scientific expertise into FDA.
- Planning a public-private collaboration to advance the science and tools necessary for generating better and more useful post-market medical evidence about FDA-regulated products.

Following a difficult launch, primarily due to the misperception that the foundation's interactions with industry would or could present a conflict of interest, RUF is primed to work in areas where it can add value to FDA. Here are some examples:

- RUF is exploring new approaches in predictive toxicology, such as using systems biology to determine the full range of effects of exposure to a toxicant. The Foundation could, for instance, take a class of drugs (protein kinase inhibitors in cancer, for example) and look at one adverse event, analyzing the data and obtaining information that would support the regulatory process.

- RUF is tackling regulatory science education questions, considering the CERSI concept and various scenarios for regulatory science professional development. In doing so, the foundation can ascertain the number of CERSIs necessary, how to make them sustainable, and how to design regulatory science educational programs that can have an impact. Further, RUF is examining whether regulatory science education might be structured as a skill-based system where scientists would be taught skill sets so that the right teams can be brought together for the right project.

- RUF is creating a research community, heavily populated by all key regulatory science stakeholders as part of the Innovation in Medical Evidence Development and Surveillance[28] (IMEDS). Structured as a public-private partnership, IMEDS addresses

[28] IMEDS webpage, http://imeds.reaganudall.org. Accessed on Sept. 9, 2015

critical needs in the continued development of methods for using electronic health data for safety assessments.

Let us consider the following scenario: today there is no definitive clinical trial data that can shed light on the potential impact of anesthetics in cognitive function when administered to young children. In studies of children, it is not clear whether the anesthetic agents, the medical conditions or the procedures requiring anesthesia may be the cause of deficits. NCTR developed compelling evidence in animals about the effects of anesthetic agents on brain-cell death and animal behavioral and cognitive function.

Manufacturers are generally unwilling to support large trials of generic drugs, and there is little FDA funding to support the studies required to obtain the information that will allow the agency, physicians, and parents to make informed decisions. To address this, in 2010 FDA formed Strategies for Mitigating Anesthesia-Related neuroToxicity in Tots (SmartTots), a partnership with the International Anesthesia Research Society, professional societies, academic research institutions, patient advocacy groups, industry, and other government and nonprofit organizations.

Although highly committed to its mandate, and with four ongoing projects that evaluate children that have received anesthesia, SmartTots has had limited success in obtaining the level of resources necessary to address this crucially important scientific question. With its fundraising capacity and the skill to bring multiple parties to the table, RUF could play a catalytic role in many initiatives.